REMARKS

Claims 1-6, 8, 10-18, 20, 22-24, 26-29, and 31-34 are pending in this application. Claims 1, 12, 26, and 31 have been amended. Support for the amendments is found in the specification and claims as filed. The amendments to Claims 1, 12, 26, and 31 were entered solely to clarify the subject matter of the claims and not specifically pursuant to any provision of the Patent Act, therefore these amendments, even if viewed as narrowing, have not been made for a reason related to patentability.

Claim Rejections - 35 U.S.C. § 103(a)

Claims 1, 4, 5, 8, 12, 13, 16, 17, 20, 26-29, and 31-34 have been rejected under 35 U.S.C. §103(a) as obvious over WO96/10374 ("WO '374") in view of U.S. 4,919,939 ("US '939"). To articulate a *prima facie* case of obviousness under 35 U.S.C. §103(a), the PTO must, *inter alia*, cite prior art that teaches or suggests all the claimed limitations. *In re Royka*, 490 F.2d 981 (C.C.P.A. 1974). Also, to establish a *prima facie* case of obviousness, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. *See, e.g.,* M.P.E.P. § 2142. As discussed below, the cited references do not teach a "stable liquid adhesive" as presently claimed in independent Claims 1 and 12. Moreover, there is no suggestion or motivation to modify or combine reference teachings to obtain a "stable liquid adhesive."

It is asserted in the Office Action that "[t]he primary reference teaches each element of the composition, except for the microencapsulation of the active agent, i.e., teaches a *liquid* composition comprising cyanoacrylate, PEG, and antibiotic ..." (page 5, final line through page 6, line 2 of the Office Action (*emphasis added*)). As Applicants have demonstrated by the experiments described in the attached Declaration of Yong-Hua Zhu, the antibiotic (when unencapsulated) reacts with the cyanoacrylate, resulting in immediate polymerization and solidification of the adhesive. Accordingly, by practicing the teachings of WO '374, a solid composition is obtained, not a stable liquid composition as claimed by Applicants in Claim 1 and Claim 12. Accordingly, WO '374 does not teach a stable liquid, but only a solid composition comprising cyanoacrylate, PEG, and antibiotic.

It is also asserted that both references are concerned with the same problem (controlled release of antibiotics) as Applicants; however, it is noted on page 11, lines 19-21, that undesired reactions between the antibiotic and cyanoacrylate is also a problem of concern to Applicants. This problem is neither identified nor addressed in either WO '374 or US '939, and there is no teaching or suggestion in either reference, aside from controlled-release properties as discussed in US '939, that a particular form of antibiotic (encapsulated or unencapsulated) would have an impact on the form of the composition (stable liquid or solid), or the antibiotic effectiveness of the composition (antibiotic activity maintained or antibiotic activity lost or impaired). Neither reference teaches or suggests the desirability of adding antibiotic in microencapsulated form to obtain a stable liquid cyanoacrylate adhesive, instead of the solid composition of WO '374. Moreover, WO '374 includes no teachings as to delivery of medicament from within the disclosed matrices – the use of a porosifying agent is only taught as a means of assisting in tissue and fluid influx into the matrix, not as a means of delivering medicament from within the matrix. One skilled in the art, attempting to prepare a stable liquid adhesive containing an antibiotic according to the teachings of WO '374, noting the incompatibility of the antibiotic and the cyanoacrylate, would be discouraged from further experimentation. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990). A *prima facie* case of obviousness therefore cannot be made.

Applicants have surprisingly discovered that stable cyanoacrylate adhesive formulations that maintain their liquid state until applied to a wound, and which maintain their antibiotic activity, can be prepared by adding antibiotic encapsulated in a microcapsule to the cyanoacrylate. "A greater than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness ... of the claims at issue." *In re Corkill*, 711 F.2d 1496, 226 USPQ 1005 (Fed. Cir. 1985). Evidence of a greater than expected result may be shown by demonstrating an effect which is greater than the sum of each of the effects taken separately (i.e., demonstrating "synergism"). *Merck & Co. Inc. v. Biocraft Laboratories Inc.*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), *cert. denied*, 493 U.S. 975 (1989). The microcapsule prevents direct contact of the antibiotic and the cyanoacrylate, thereby 1) preventing premature polymerization and solidification of the cyanoacrylate by the antibiotic, and 2) preventing loss of antibiotic activity by reaction of the antibiotic with the cyanoacrylate. Hence, Applicants' adhesive is a

stable liquid, and not the solid composition taught by the WO '374. Moreover, the antibiotic in Applicants' adhesive maintains its antibiotic activity, unlike the antibiotic of the WO '374, which loses antibiotic activity due to reaction between the antibiotic and the cyanoacrylate.

Neither WO '374 nor US '939 even recognizes that premature polymerization or deactivation of the antibiotic is an issue when antibiotics are mixed with a cyanoacrylate, much less teaches an effective way of overcoming this incompatibility such that a stable liquid adhesive for sealing a wound comprising a cyanoacrylate, a therapeutic agent comprising an antibiotic encapsulated in a microcapsule, and a defect forming agent can be prepared. A *prima facie* case of obviousness therefore cannot be made, and Applicants respectfully request that the rejection be withdrawn.

Claim Rejections - 35 U.S.C. § 103(a)

Claims 2, 3, 14, and 15 have been rejected under 35 U.S.C. §103(a) as obvious over WO '374 in view of US '939 and further in view of US 5,811,091 ("US '091").

As discussed above, WO '374 and US '939, either alone or in combination, do not teach or suggest the invention as presently claimed. US '091 includes no additional disclosure overcoming the deficiencies of WO '374 and US '939. US '939 merely teaches that butyl cyanoacrylates and octyl cyanoacrylates can be employed adhesives for sealing wounds. US '939 does not include any teachings as to preparation of a stable liquid adhesive for sealing a wound comprising a cyanoacrylate, a therapeutic agent comprising an antibiotic encapsulated in a microcapsule, and a defect forming agent.

Accordingly, Applicants respectfully request that the rejection be withdrawn.

Claim Rejections - 35 U.S.C. § 103(a)

Claims 2, 3, 10, 11, 14, 15, and 22-24 have been rejected under 35 U.S.C. §103(a) as obvious over WO '374 in view of US '939 and further in view of WO96/00760 ("WO '760").

As discussed above, WO '374 does not teach or suggest the invention as presently claimed. WO '760 includes no additional disclosure overcoming the deficiencies of WO '374. WO '760 discloses biomedical adhesives comprising a biocompatible pH modifier (e.g., a

microencapsulated pH modifier). WO '760 does not include any teachings as to preparation of a stable liquid adhesive for sealing a wound comprising a cyanoacrylate, a therapeutic agent comprising an antibiotic encapsulated in a microcapsule, and a defect forming agent.

Accordingly, Applicants respectfully request that the rejection be withdrawn.

Claim Rejections - 35 U.S.C. § 103(a)

Claims 6 and 18 have been rejected under 35 U.S.C. §103(a) as obvious over WO '374 in view of US '939 and further in view of WO99/20685 ("WO '685").

As discussed above, WO '374 does not teach or suggest the invention as presently claimed. WO '685 includes no additional disclosure overcoming the deficiencies of WO '374. WO '685 merely discloses coating formulations for sustained-release drug implants that include pore forming agents, but does not disclose an adhesive comprising a microencapsulated therapeutic agent in combination with a cyanoacrylate and a water soluble defect forming agent. WO '685 does not include any teachings as to preparation of a stable liquid adhesive for sealing a wound comprising a cyanoacrylate, a therapeutic agent comprising an antibiotic encapsulated in a microcapsule, and a defect forming agent.

Accordingly, Applicants respectfully request that the rejection be withdrawn.

Comments on Examiner's Response to Amendment

The Office Action refers to US 6,207,193 to Pellegrini ("US '193") for the proposition that the result of encapsulation as to block the undesired polymerization of cyanoacrylate is obvious and is expected to protect cyanoacrylate from contact with the active agents. However, US '193 states that "[e]ach of the components of the drug delivery system of the invention; i.e., the drug or therapeutic agent, the carbohydrate, the cyanoacrylate ester and, optionally, the plasticizer and polymerization inhibitor, are inert with respect to one another so that there is no interaction between them, even when they are exposed to moisture." This passage of US '193, requiring components be inert with respect to one another, implies that encapsulation is insufficient to block any undesired polymerization of cyanoacrylate by an encapsulated active agent. Hence, it teaches away from Applicants' invention.

Conclusion

In view of the foregoing amendments and remarks, it is respectfully submitted that the present application is in condition for allowance. Should the Examiner have any remaining concerns that might prevent the prompt allowance of the application, the Examiner is respectfully invited to contact the undersigned at the telephone number below.

Respectfully submitted,

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Dated: 4/7/05

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